INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/000032

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07K14/525, A61K38/00, 47/48//C12N15/09

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07K14/525, A61K38/00, 47/48, C12N15/09

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY(STN), BIOSIS/MEDLINE/WPIDS/BIOTECHABS/CA(STN), JICST FILE(JOIS)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5606023 A (Thomas Jefferson University), 25 February, 1997 (25.02.97), (Family: none)	1,2,4,6-8
Y	Loetscher H. et al., Human tumor necrosis factor alpha (TNF alpha) mutants with exclusive specificity for the 55-kDa or 75-kDa TNF receptors, J.Biol.Chem., 1993, Vol.268, pages 26350 to 26357	1,2,4,6-8
Y	Yasuo Tsutusmi et al., "Phage Hyomen Teijiho o Kushishita Kinosei Jinko Tanpakushitsu no Soshutsu to DDS eno Tenkai", Drug Delivery System, 2003, Vol.18, pages 536 to 544	1,2,4,6-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 April, 2005 (06.04.05)	19 April, 2005 (19.04.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Claim 1 involves a plural number of tumor necrosis factor mutant proteins which are common to each other in binding specifically to TNF-R1 or TNF-R2 and divided into those having an antagonism to tumor necrosis factor and those having an agonism to tumor necrosis factor. Since there has been reported by, for example, document JP 7-285997 A an agonist specifically binding to TNF-R1 which is a tumor necrosis factor mutant protein having substitution at the amino acid residue at the 86-position "from the N-end in the amino acid sequence represented by SEQ ID NO:1 in Sequence Listing", "binding specifically to either TNF-R1 or TNF-R2" cannot be considered as a technical feature making a contribution over prior art. (continued to extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

The parts relating to a tumor necrosis factor mutant protein having an antagonism in claims 1, 6 and 7 and claims 2, 4 and 8.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box No.III of continuation of first sheet(2)

Such being the case, the tumor necrosis factor mutant proteins involved in claim 1 are not considered as being so linked as to form a single general inventive concept.

Also, claim 3 involves a plural number of tumor necrosis factor mutant proteins which are common to each other in specifically binding to either TNF-R1 or TNF-R2 and having an agonism to tumor necrosis factor. However, there has been already known an agonist specifically binding to TNF-R1 which is a tumor necrosis factor mutant protein having substitution at the amino acid residue at the 86-position "from the N-end in the amino acid sequence represented by SEQ ID NO:1 in Sequence Listing" as described above, "being an agonist binding specifically to either TNF-R1 or TNF-R2" cannot be considered as a technical feature making a contribution over prior art. Such being the case, the tumor necrosis factor mutant proteins involved in claim 3 are not considered as being so linked as to form a single general inventive concept.

The same applied to claim 5, too.

Thus, claims 1 to 9 have 24 inventions including the invention relating to an antagonist binding specifically to either TNF-R1 or TNF-R2 and the inventions relating respectively to the amino acid sequences represented by SEQ ID NOS:37 to 59.